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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/254,623	07/08/99	SHANAHAN-PRENDERGAST E	8007-7064 US

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1642	17

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

PTO-90C (Rev.11/00)

1- File Copy

Office Action Summary

Application No.	Applicant(s)
09/254,623	Shanahan-Prendergast, E

Examiner	Art Unit
Minh-Tam Davis	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jun 18, 2001* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-124* is/are pending in the application.

4a) Of the above, claim(s) *1-4, 6-42, 45, and 48-124* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *5, 43, 44, 46, and 47* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *? sheets*

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

Applicant's election with traverse of group V, claims 5, 45 and 46, in Paper No. 16 is acknowledged. In a telephone conversation with Kevin Brown on 07/27/01 species phospholipase A2 type I, and mammalian phospholipase A2 were elected. The traversal is on the ground(s) that 1) claims 43, 44 and 57 depend on claim 5 and thus cannot be said to be independent and distinct relative to the subject matter of claim 5 and should be examined in the present application, in order to conserve US Patent and Trademark office resources, and because doing so would not place an undue burden on the Examiner, 2) In addition, the subject matter of groups XXI, XXXIV, XXXVII, and XXXXXXX is sufficiently related to that of group V that there would not be an undue burden for the Examiner to search and examine these groups together with group V, 3) During international stage, it was found that there exists unity of invention among all the subject matter of the claims pending, 4) A single generic claim that is required to be divided up and presented in several applications would never be considered on its merits. This is not found persuasive because of the following reasons: 1) Group XXI, drawn to a composition comprising mammalian, plant or insect phospholipase A2 and phospholipase C enzyme, is distinct from the method of preventing neoplasm of the instant application as product and process. Further, there is no special technical feature linking the two groups, because phospholipase A2 is known in the art, (Murakami M et al, 1992, Advances Exp. Med Biol, 318: 27-34, and Menez et al, EP 0322262, 28/06/89) and thus is not unique to the claimed invention. 2) Group XXXIV, drawn to a method of inoculation with two or more phospholipase A2 enzyme

types, is patentably distinct from the the method of preventing neoplasm of the instant application, using only one type of phospholipase A2, because different phospholipase A2 types have different molecular weights and different properties, e.g. acid or neutral or basic or highly basic, with or without toxicity properties, wherein only the highly basic phospholipase A2 has been shown to be toxic and could be used to treat cancer when complexed with crotoxin A (specification, page 2, second paragraph, Menez et al, EP 0322262, 28/06/89, Plata et al, PN=5,164,196). Thus the results from administration of two types of phospholipase A2, e.g. acid and neutral phospholipase A2, could not be predicted from the results from administration of only one type of phospholipase A2, such as basic phospholipase A2. 3) Group XXXVII, drawn to a method of preventing neoplastic development, comprising administering phospholipase A2 in combination with anti-inflammatory agents, is distinct from the instant application, because the method of group XXXVII, not only related to the use of a compound for preventing cancer but also a compound for treating inflammation, wherein inflammation is a different event than cancer development, and is not necessarily related to cancer development. 4) Group XXXXXXX, drawn to a method for treating diseases, comprising administering venom, is distinct from the instant application, because although venom contains phospholipase A2, venom also comprises a complex mixture of many substances such as toxins, enzymes, growth factors, activators and inhibitors with wide spectrum of biological activities, including the cytolytic atroporin and kaotree, which could selectively kill tumor cells, and which have a molecular weight of 35,000 and 6000 daltons, respectively, and

thus are different from the claimed phospholipase A2 (Lipps et al, PN=5,565,431, abstract and column 1, last paragraph).

After review and reconsideration, claims 43, 44, and 57 however are rejoined with group V, claims 5, and 46, wherein claim 43 is examined only in the context of other therapeutically effective agents which are adjuvants, and not anti-inflammatory agent. Claim 45 is not examined, because it is drawn to a method of preventing cancer using venom, which is not the same as phospholipase A2 alone or with adjuvants.

The requirement is still deemed proper and is therefore made FINAL.

Accordingly, claims 5, 43, 44 and 46-47, species phospholipase A2 type I, and mammalian phospholipase A2 are examined in the instant application.

REJECTION UNDER 35 USC 112, SECOND PARAGRAPH

Claims 5, 43, 44 and 46-47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 5, 43, 44 and 46-47 are indefinite for the use of the abbreviated language "PLA2" in claim 5, which is not commonly known in the art. This rejection could be obviated by, for example, replacing PLA2 with phospholipase A2.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, ENABLEMENT

Claims 5, 43, 44 and 46-47 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 5, 43, 44 and 46-47 are drawn to a method of preventing neoplastic development, comprising administering a therapeutic vaccine containing mammalian, plant or insect phospholipase A2 or part thereof as the principal antigen component, or comprising administering said vaccine and adjuvants.

The specification discloses that phospholipase A2 are lipolytic enzymes that hydrolyze the sn-2-acylester bond in glycerophospholipid (p.2, second paragraph). The specification discloses that elevated local and circulating levels of phospholipase A2 is a very early indication of neoplastic development prior to tumor mass (p.3, first paragraph), and that altered cytosolic phospholipase A2 activity or defects in its control and regulation is a predisposing factor to causing tumor cell development (p.3, paragraph before last). The specification further discloses that anti-serum to snake venom inhibits phospholipase A2 isolated from human synovial fluid (p.8-9), and that administration of anti-serum to snake venom to mice carrying melanoma reduces tumor size as compared to the control (p.11-12) . In addition, the specification discloses that Russelli vipera venom entrapped in liposomes and porcine phospholipase A2 entrapped in liposomes working in combination were used to immunize mice on the first day and day 3, respectively, with booster of each vaccine at 3 weeks interval. The mice are challenged on day 30

with leukemic cells. The vaccinated mice have 100% survival rate as compared to the control untreated mice, all of which died within 24 days after the injection of leukemic cells (p.14-15). The specification speculates that anti-serum to snake venom and/or phospholipase A2 are thus active anti-tumor proliferation compounds and immune enhancing (p.6, paragraph before last). The specification further speculates that anti-serum to phospholipase A2 can be applied as a prophylactic therapy by using phospholipase A2 or synthetic peptides having phospholipase A2 to stimulate an immunoglobulin response within a patient (p.7, last paragraph).

One cannot extrapolate the teaching in the specification to the claims for the following reasons. 1) It is not clear whether Russelli vipera venom entrapped in liposomes and porcine phospholipase A2 entrapped in liposomes could prevent tumor development in mice having leukemia, because although the mice are challenged on day 30 with leukemic cells, and that said mice had been previously treated with the venom and porcine phospholipase A2 on first day and day 3 respectively, the pretreated mice also receive booster of vaccines every 3 weeks, i.e. approximately on day 21 or 24, and on day 42 or 45, or 12 or 15 days after the challenge of leukemia cells on day 30. It is possible that the booster vaccines kill the tumor cells that have been grown from the injected leukemia cells on day 30, and not the first vaccines on the first day and day 3 that prevent the development of leukemia, because it is known in the art that snake venom contains several toxins, such as atroporin, kaotree, crotoxin, that are able to selectively kill various types of cancer cells both *in vitro* and *in vivo* (Lipss et al, PN=5,565,431 and Plata et al,

PN=5,164,196). In other words, the example on pages 14-15 discloses a method of treating already existing tumor cells, rather than a method of preventing neoplasm development.

Further, as written the claims encompass a method for preventing neoplastic development from a normal human, without any tumor. The example in the specification only discloses the inhibition of growth of leukemic cells, or killing of leukemic cells that are injected into mice, not preventing development of cancer from normal cells. The life span of human is much longer than that of mouse. Although in model rat and mouse, the time period when the animal, which is at risk of developing cancer, develops cancer is known, it is not the case in human. That is it is not known when a human who is at risk of developing cancer would start to develop cancer. Therefore, it is unpredictable when and for how long one of skill in the art should administer the claimed phospholipase A2 for preventing cancer development. Furthermore, if phospholipase A2 is injected continuously during all the life span of human, severe side effects and toxicity could develop and thus preventing the success of the action of phospholipase A2, because several forms of phospholipase A2 are known to be toxic ((Menez et al, EP 0322262, 28/06/89, Plata et al, PN=5,164,196). Usually the toxicity data is not required, however if success of the action of phospholipase A2 is prevented by evere toxicity, such data is necessary. Yet the specification lacks guidance as how to prevent cancer development in human at risk of developing said tumor or how to prevent cancer in patients who have had said tumor. That is the specification lacks guidance on dosage, frequency of treatment and assessment of disease progression in human. Furthermore, the specification lacks description of how to assess human in risk of developing

tumor, e.g. assessment based on family health history and genetic screening of said individual at risk of tumor development

Moreover, the claims are drawn to a method for preventing neoplasm development by injection of phospholipase A2 alone or together with an adjuvant, but not in combination with venom, as disclosed in the specification. It is unpredictable that phospholipase A2 alone would be able to kill starting tumor cells and consequently prevent development of tumor mass from starting tumor cells, because it is known in the art that snake venom contains several toxins, such as atroporin, kaotree, crotoxin, that are able to selectively kill various types of cancer cells both *in vitro* and *in vivo* (Lipss et al, PN=5,565,431 and Plata et al, PN=5,164,196). Thus the tumor cell killing by a combination of a venom and phospholipase A2 as disclosed in an example on pages 14-15 could be due solely to the toxins in the venom, and not to phospholipase A2. Further, one of skill in the art would not have expected that phospholipase A2 alone could kill or prevent development of tumor mass from starting tumor cells, due to either the cytotoxicity of the basic phospholipase A2 or the production of antibodies that suppress the activity of phospholipase A2, as speculated by the specification. Concerning killing of starting tumor cells due to the cytotoxicity of basic phospholipase A2, although basic phospholipase A2 when complexed with crotoxin A could selectively kill some tumor cells, one of skill in the art would have expected that the basic phospholipase A2 alone (or crotoxin B) would not be effective in killing tumor cells *in vivo*, because of non-specific absorption of the basic phospholipase A2 to many acidic tissue constituents in the absence of crotoxin A (Plata et al, *supra*, column 8, second paragraph).

Moreover, concerning killing of starting tumor cells due to the production of antibodies against phospholipase A2 activity by administration of phospholipase A2, as speculated by the specification, there is no correlation between reduced phospholipase A2 activity and cancer development, because phospholipase A2 is only known to be a lipolytic enzyme that hydrolyzes the sn-2-acylester bond in glycerophospholipid. Although the specification discloses that elevated local and circulating levels of phospholipase A2 is a very early indication of neoplastic development prior to tumor mass (p.3, first paragraph), and that altered cytosolic phospholipase A2 activity or defects in its control and regulation is a predisposing factor to causing tumor cell development, Applicant has not shown that increased local and circulating levels of phospholipase A2 is responsible for tumor development. Further, there is no data showing that altered cytosolic phospholipase A2 activity or defects in its control and regulation is a predisposing factor to causing tumor cell development. Moreover, even if altered cytosolic phospholipase A2 activity or defects in its control and regulation is a predisposing factor to causing tumor cell development, it is not clear what kind of alteration of cytosolic phospholipase A2 activity is referred to, and it is questionable that reduction of phospholipase A2 activity by anti-phospholipase A2 antibodies would alleviate the alteration of cytosolic phospholipase A2 activity or defects in its control and regulation. In addition, although anti-serum to venom could reduce phospholipase A2 activity, and anti-serum to venom could kill tumor cells, as disclosed by the specification, it is not necessary that the killing of tumor cells by anti-serum to venom is due to the presence of antagonist antibodies that reduce the activity of phospholipase A2 activity, because venom also

comprises a complex mixture of many substances such as toxins, enzymes, growth factors, activators and inhibitors with wide spectrum of biological activities, and it is unpredictable which factors in the anti-venom serum is responsible for reduction of phospholipase A2 activity (Lipps et al, PN=5,565,431, abstract and column 1, last paragraph). Further, it is well known in the art that there exist different types of antibodies, including agonists and antigonists, and thus injection of phospholipase A2 does not necessarily elicit the production of antagonist antibodies that reduce phospholipase A2 activity. The site of the activity of phospholipase A2 is not known, and it is unpredictable that said site is exposed such that antagonist antibodies against the activity of phospholipase A2 could bind to phospholipase A2, and inhibit its activity.

In view of the above, undue experimentation woud be required to practice the claimed invention.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE

1. If Applicant could overcome the above 112, first paragraph rejection, claims 5, 43, 44 and 46-47 are still rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of preventing neoplastic development comprising administering porcine phospholipase A2, does not reasonably provide enablement for a method of preventing neoplastic development comprising administering "part" of phospholipase A2 as the principal antigen component. The specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 5, 43, 44 and 46-47 are drawn to a method of preventing neoplastic development, comprising administering a therapeutic vaccine containing mammalian, plant or insect phospholipase A2 or "part" thereof as the principal antigen component, or comprising administering said vaccine and adjuvants.

The specification contemplates the administration of phospholipase A2 or synthetic peptides demonstrating phospholipase A2 activity plus adjuvant to stimulate an immunoglobulin response within a patient (p.7, last paragraph).

It is noted that part of phospholipase A2 could be as little as one or two amino acids. Further, there is insufficient guidance regarding the parameters and sequence of peptides which has phospholipase A2 activity and which has the ability to produce antagonist antibodies specific for phospholipase A2. There is insufficient guidance regarding selection of peptides that meet the instant criteria of generating CTLs. It would not be possible to determine with any predictability whether the antibodies produced from such fragments actually bind to phospholipase A2. It is well known in the art that when using synthetic amino acid sequences as immunogens to develop antibodies, one cannot be certain how well exposed such a peptide is nor how immunogenic it is. Furthermore, this does not take into account the 3 dimensional folding of the native molecule, nor its glycosylation or other post-translational modifications and other characteristics which are of significant importance in an antibody response. Peptides or synthetic antigens cannot effectively

substitute for the natural tertiary and quarterary structure of a protein in a physiological situation. Further, there is no teaching in the specification of which part of the protein should be used to produce antibodies which will bind specifically to phospholipase A2. Since detailed information regarding the structural, and functional requirements and properties of the claimed " part of phospholipase A2" are lacking, it would be undue experimentation for one of ordinary skill in the art to make and use the invention.

Moreover, as written, 5, 43, 44 and 46-47 drawn to a method of preventing neoplastic development, comprising administering part of phospholipase A2 as the principal antigen component, together with adjuvants encompasses claims to defining epitopes specific for a polypeptide. However, there is no teaching in the specification of whether or not the epitopes are linear or comprise 3-dimensional structures. Herbert et al. (The Dictionary of Immunology, Academic Press, 4th edition, 1995, p.58) define epitopes as the region on an antigen molecule to which antibody or the T cell receptor binds specifically wherein the 3-dimensional structure of the protein molecule may be essential for antibody binding. However, the specification fails to disclose sufficient guidance and objective evidence as to the linear and or three-dimensional conformation of the polypeptide fragments which constitute epitopes recognized by the claimed invention. Antibodies bind to structural shapes that may be linear stretches of amino acids, conformational determinants formed by the folding of peptides, carbohydrate moieties, phosphate or lipid residues or a combination thereof. Moreover, as evidenced by Greenspan et al., defining epitopes is not as easy as it seems (Nature Biotechnology 7:936-937 (1999). Even when the

epitope is defined, in terms of the spatial organization of residues making contact with ligand, then a structural characterization of the molecular interface for binding is necessary to define the boundaries of the epitope (page 937, 2nd column).

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art on how to use the claimed method employing the claimed part of phospholipase A2. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth, and it cannot be predicted from the disclosure how to use the encompassed fragments. Therefore, undue experimentation would be required to enable the claims as written.

2. If Applicant could overcome the above 112, first paragraph rejection, claims 5, 43, 44 and 46-47 are still rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of preventing neoplastic development comprising administering porcine phospholipase A2, does not reasonably provide enablement for a method of preventing neoplastic development comprising administering any type of phospholipase A2 as the principal antigen component. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 5, 43, 44 and 46-47 are drawn to a method of preventing neoplastic development, comprising administering a therapeutic vaccine containing mammalian, plant or insect

phospholipase A2 or "part" thereof as the principal antigen component, or comprising administering said vaccine and adjuvants.

The specification discloses administration of snake venom and porcine phospholipase A2, each component is entrapped in liposome (p.14, 15).

One cannot extrapolate the teaching in the specification to the claimed invention. It is well known in the art, and as disclosed in the specification, there are different phospholipase A2 types having different molecular weights and different properties, e.g. acid or neutral or basic or highly basic, with or without toxicity properties, wherein the highly basic phospholipase A2 has non-specific absorption to many acidic tissue constituents when not complexed with crotoxin A (specification, page 2, second paragraph, Menez et al, EP 0322262, 28/06/89, page 3, 4th paragraph, Plata et al, PN=5,164,196, column 8, second paragraph). Thus it is highly unlikely that the basic phospholipase A2 would be suitable for use in the claimed method, because it would not be sufficiently delivered to target cells for making antibodies, when administered alone without crotoxin A. Further, there is another group of highly toxic phospholipase A2, found in many snake venom, that cause rapid paralysis by blocking the release of acetylcholine in the area of pre-synaptic terminals (Menez et al, EP 0322262, 28/06/89, page 3, 4th paragraph). This group of highly toxic phospholipase A2 would be too toxic and thus unsuitable for use in preventing neoplastic development.

In view of the above, undue experimentation woud be required to practice the claimed invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Minh-Tam B. Davis whose telephone number is (703) 305-2008. The examiner can normally be reached on Monday-Friday from 9:30am to 3:30pm, except on Wesnesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Tony Caputa, can be reached on (703) 308-3995. The fax phone number for this Group is (703) 308-4227.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0916.

Minh-Tam B. Davis

July 20, 2001

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